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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/625,152	07/23/2003	David B. Agus	67789-19	1369

50670 7590 02/09/2007

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EXAMINER	
ANDERSON, JAMES D	
ART UNIT	PAPER NUMBER
1614	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/09/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/625,152	AGUS, DAVID B.	
	Examiner	Art Unit	
	James D. Anderson	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-12,15-23,25,26,28,29,31,32,34 and 57-88* is/are pending in the application.

4a) Of the above claim(s) *10,29,31,32,34,67-70 and 81-84* is/are withdrawn from consideration.

5)☒ Claim(s) *73,74,77,78,85 and 86* is/are allowed.

6)☒ Claim(s) *1,4,5,8,9,11,12,15-23,26,28,57-63,65,66,71,72,75,76,79,80,87 and 88* is/are rejected.

7)☒ Claim(s) *6,7,25 and 64* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

Applicant's request for reconsideration of the finality of the rejection of the last Office action is persuasive and, therefore, the finality of that action is withdrawn.

Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn. However, upon further consideration the following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Applicant's amendment filed 11/28/2006 has been entered in to the record.

Status of the Claims

Claims 1, 4-12, 15-23, 25-26, 28-29, 31-32, 34 and 57-88 are currently pending and are the subject of this Office Action. Claims 10, 29, 31-32, 34, 67-70 and 81-84 are withdrawn from consideration (the claims recite a non-elected species).

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. § 119(e) or under 35 U.S.C. § 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. § 120 as follows:

The later-filed application must be an application for a patent for an invention, which is also disclosed in the prior application (the parent or original nonprovisional application or

provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. § 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 10/142,087, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. § 112 for one or more claims of this application. The limitations of the instant claims do not have support in the '087 application. For example, no support was found in prior filed U.S. Provisional Application No. 60/290,307, filed May 10, 2001 or prior filed U.S. Non-Provisional Application No. 10/142,087, filed May 9, 2002, for the following limitations of the instant claims: 1) claims reciting a dose range of 180 to 300 mg per day of the claimed compounds; 2) claims reciting the administration of an estrogen lowering drug; and 3) the prodrug formulas recited in claims 12, 60, 75 and 87.

As such, the earliest effective U.S. filing date afforded the instant claims has been determined to be 7/23/2003, the filing date of the instant application. Because the instant claims are not entitled to the filing date of any prior filed applications, additional prior art rejections are warranted.

Claim Rejections - 35 USC § 112 (1st Paragraph)

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12, 15-22, 26, 28, 60-62, 65-66, 72, 75-76, 79-80 and 87-88 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a Written Description rejection.

The specification discloses prodrugs having formula IV on pages 7-8 of the specification and hydroxy protecting groups on page 8 of the specification, which provides written description for prodrugs having formula IV and the specific hydroxy protecting groups recited in the specification. Said description also supports a chemical material of the instant invention sufficiently as to written description for compounds which also possess the functional requirements cited in various instant claims.

However, claims 12, 15-22, 60-62, 72, 75-76 and 87-88 encompass a broad class of "hydroxy protecting group[s]" of vast structural diversity without a limitation other than the fact that they are attached to an oxygen atom and without correlation of any functional requirements. None of these structurally diverse "hydroxy protecting groups" meet the written description provision of 35 USC § 112, first paragraph, except those recited in the specification at, for example, page 8 as filed. The specification provides insufficient written description to support the genus encompassed by the claims.

Similarly, claims 26, 28, 65-66, 79-80 and 83-84 encompass a broad class of "prodrug[s]" of the recited compounds without limitation or description of any structural features

of said prodrugs. Thus, the broad recitation of "prodrug" has insufficient written description to support the genus encompassed by the claims.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116.)

With the exception of prodrugs having Formula IV (page 7 of specification) and the explicitly recited hydroxy protecting groups (page 8 of specification), the skilled artisan cannot envision the detailed chemical structure of the encompassed chemicals, regardless of the complexity or simplicity of the method of isolation or identification. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The chemical itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmacentical Co.* Ltd., 18 USPQ2d 1016. In *Fiddes v. Baird*, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provides only the bovine sequence.

Finally, *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1404, 1405 held that: ...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565,

1572, 41 USPQ2d 1961, 1966 (i997); *In re Gostefi* , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966.

Therefore, only claims limited to prodrugs having Formula IV and specific hydroxy protecting groups, but not the full breadth of the broadly worded claims meet the written description provision of 35 USC § 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant and not connected with functional limitations in the instant claims. For example, in the instant claims the compounds must be inhibitory of tumor cell growth. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC § 112 is severable from its enablement provision. (See page 1115).

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 4-5, 8-9, 11, 23, 57-59, 63 and 71 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Kim *et al.* (Cancer Research, 2002, vol. 62, pages 5365-5369) (prior art of record).

The instant claims are drawn to methods of treating androgen-independent prostate cancer comprising administering raloxifene.

Kim *et al.* disclose that raloxifene induces apoptosis in androgen-independent human prostate cancer cell lines (Abstract). Raloxifene is a selective estrogen receptor modulator (SERM) that binds to both estrogen receptor-α (ER-α) and estrogen receptor-β (ER-β) with high affinity (page 5365, right column). The binding affinity of raloxifene to ER-α is four times higher than to ER-β (*id.*). Increased expression of ER-α has been associated with prostate cancer progression, metastasis and hormone-refractory phenotype (*id.*). Prior art observations "suggest that ER is a reasonable target for therapeutic intervention in prostate cancer patients" (*id.*). Thus, the authors examined the effects of raloxifene in androgen-independent human prostate cancer cell lines. PC3, PC3M and DU145 androgen-independent prostate cancer cell lines were shown to all express ER-β, whereas only PC3 and PC3M cells expressed ER-α (page 5366, right column). Raloxifene inhibited the proliferation of all three prostate cancer cell lines in a dose-dependent manner (*id.*, Figure 1). Raloxifene was also shown to induce apoptosis of PC3 and DU145 prostate cancer cells (page 5367, Figure 3 and page 5368, Figure 4). The authors conclude that the consistent expression of ERs in human prostate cancer cell lines suggests that estrogen/ERs may be potential targets for therapeutic intervention in prostate cancer patients (page 5368, right column). The concentration of raloxifene used in the majority of the studies was 10^{-6} M. Clinical trials have shown that the serum concentration of raloxifene is in the 10^{-9} M range when administered at the currently recommended dose of 30-150 mg/day (page 5369, left column). As such, the authors suggest that 10^{-6} M may not be an achievable concentration *in*

vivo. However, the effect of raloxifene was observed initially in prostate cancer cell lines at 10^{-9} M after 4 days of treatment (*id.*).

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

In the instant case, the prior art discloses raloxifene is effective in inhibiting androgen-independent prostate cancer cell proliferation and inducing apoptosis of said cells. Kim *et al.* also provide the skilled artisan with the motivation to administer SERMs to treat prostate cancer (*i.e.* expression of ER-α and ER-β in prostate cancer cells). The instant claims differ from the prior art in that they claim the treatment of mammals with a specific dose range of raloxifene.

In view of the above prior art disclosure and analysis, the instantly claimed method of treating androgen-independent prostate cancer by administering raloxifene would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. The skilled artisan would have been imbued with at least a reasonable expectation that raloxifene would be effective in treating prostate cancer given the disclosure of Kim *et al.* Further, the instantly claimed doses could have been readily determined by one of ordinary skill in the art through routine experimentation. In fact, Kim *et al.* suggest that a dose of more than 150 mg/day may be needed.

Claims 1, 4-5, 8-9, 11, 23, 57-59, 63 and 71 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Steiner *et al.* (U.S. Patent No. 6,632,447) (prior art of record).

Steiner *et al.* disclose the use of antiestrogens, including raloxifene, for the prevention and treatment of prostate cancer (Abstract; Claims; col. 4, lines 7-8). The compositions for the prevention or treatment of prostate cancer can be administered in a range of 5 to 80 mg/day (col. 6, lines 18-19) and can be administered orally (col. 6, lines 27-29).

One skilled in the art would appreciate that "prostate cancer", when used in Steiner, includes both androgen-dependent and androgen-independent prostate cancer. Steiner *et al.* recognize the two types of prostate cancer wherein they state:

> Hormone therapy remains the standard method of treatment of recurrent and advanced prostate cancer despite the common development of hormone refractory disease. Therefore, new approaches for the prevention and treatment of prostate cancer are needed to accommodate the increasing number of men diagnosed with the disease. Steiner et al., Column 14, Lines 9-15.

Thus, the skilled artisan would recognize that the methods disclosed in Steiner *et al.* could be used to treat androgen-independent prostate cancer.

Steiner clearly discloses the treatment of prostate cancer, including androgen-independent prostate cancer (as discussed *supra*). Steiner discloses that the chemopreventative agent prevents, prevents reoccurrence of, suppresses and inhibits prostate carcinogenesis but also treats prostate cancer (Abstract). Clearly, treating prostate cancer is a separate concept in Steiner, not meant to be commensurate with prevention. Further evidence of this is found in column 3, lines 1-6 of Steiner wherein it is taught that:

> This invention relates to a method of treating a subject *with* prostate cancer comprising: administering to a mammal subject, a pharmaceutical preparation comprising an anti-estrogen, or its analog, derivative, isomer, and metabolite thereof, and their pharmaceutically acceptable salts, esters, or N-oxides, and mixtures thereof.

Clearly, "a subject with prostate cancer" is in need of a treatment, not prevention. Column 5, line 17 also discusses the "treatment of prostate cancer". A "method of treating a subject with prostate cancer" is taught in Claim 2 (col. 17, lines 9-14). Although the examples in Steiner are limited to the prevention of prostate cancer, one skilled in the art would appreciate that treatment of prostate cancer taught in Steiner *et al.* would include stabilizing or reducing primary tumor mass.

Steiner *et al.* only define a limited range of doses (*i.e.* 5-80 mg/day). However, optimization of doses effective to elicit a preferred pharmacological effect is routine in the art of chemotherapy. As such, it would have been obvious to the skilled artisan to use higher doses than those disclosed in Steiner *et al.* if the initial doses were ineffective in treating androgen-independent prostate cancer. This is supported by the fact that instant claim 5 recites the administration of 180 mg/day only after a mammal fails to respond to an amount of 60 mg/day.

Thus, the administration of raloxifene to treat androgen-independent prostate cancer would have been prima facie obvious to the skilled artisan in view of the Steiner *et al.* patent. The skilled artisan, through routine experimentation, would readily determine the instantly claimed dose range. Further, the skilled artisan would have been imbued with at least a

reasonable expectation that doses higher than those disclosed in Steiner *et al.* would also be effective in treating androgen-independent prostate cancer.

Allowable Subject Matter

Claims 73, 74, 77, 78, 85 and 86 are allowable over the prior art.

Claims 6, 7, 25 and 64 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Anderson whose telephone number is 571-272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would

like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

James D. Anderson, Ph.D.
Patent Examiner
AU 1614

February 6, 2007

Phyllis Spivack
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PRIMARY EXAMINER
2/6/07